Assessing the Efficacy and Safety of Low-Dose Vitamin K for Reversal of INR in LVAD Patients

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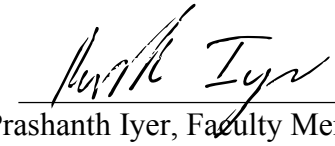

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Assessing the Efficacy and Safety of Low-Dose Vitamin K for Reversal of INR in LVAD Patients

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Abstract

Introduction: Continuous-flow left ventricular assist device (CF-LVAD) patients require warfarin, a vitamin K antagonist, as an anticoagulant to prevent thromboembolic events. LVAD patients that present with bleeding requiring a non-emergent procedure (ie. endoscopy) often require an international normalized ratio (INR) <2 to avoid potential procedural bleeding complications. The efficacy of high-dose intravenous (IV) vitamin K has been established for emergent INR reversal, but there are currently no studies that compare efficacy and safety of low-dose IV vitamin K (<5 mg) to "watchful waiting" for procedural, non-emergent INR reversal.

Hypothesis: Low-dose IV vitamin K (<5 mg) will be as safe and more effective compared to "watchful waiting," for INR reversal in patients presenting with non-emergent bleeding or in need of invasive procedures.

Methods: We conducted a single-center, retrospective cohort analysis comparing low-dose IV vitamin K to "watchful waiting" in 121 LVAD patients. Baseline characteristics such as LVAD type, baseline INR (median and IQR), and vitamin K dose were collected. Primary endpoints included thrombotic and bleeding events within 90 days of discharge and number of patients with INR <2 within 24 hours of intervention. Secondary endpoints include procedural blood loss and length of hospital stay (days). Analyses was conducted using descriptive statistics, Fischer Exact, Mann-Whitney U, and chi-squared tests.

Results: Patients in the IV vitamin K group had no thrombotic events compared to 23% of patients in the "watchful waiting" group (p=0.085). There were 38.5% and 11.8% bleeding event rates in the Vitamin K and "watchful waiting" groups, respectively (p=0.091). Patients receiving Vitamin K were more likely to have an INR <2 on days 1 and 2 compared to "watchful waiting" (p=0.046). From days 0 to 1, there was a decrease in median INR from 3.42 to 1.61 and 2.47 to 2.17 in the Vitamin K and "watchful waiting" group respectively (p=<0.01).

Conclusion: Using IV vitamin K to reverse warfarin prior to a non-emergent procedure was as safe as and more efficacious than "watchful waiting" alone. The major limitation of this study is its retrospective, non-randomized nature. Future prospective evaluation with a randomized controlled trial will be needed to corroborate these findings.

Key Words: heart assist device, warfarin, international normalized ratio, anticoagulation

Introduction

There are approximately 2500 continuous-flow left ventricular assist device (CF-LVADs) implantations each year in the United States.[1] Patients receiving CF-LVADs are at risk of developing pump thrombosis and require anticoagulation with warfarin, titrated to achieve a goal international normalized ratio (INR) of 2-3.[2–5] Previous studies have demonstrated that patients with CF-LVADs spend less time in therapeutic range and are at an increased risk for bleeding and thrombotic complications.[6,7] Bleeding is one of the most frequent complications with CF-LVADs occurring in 30% to 60% of patients that increase morbidity and mortality.[8] In particular, gastrointestinal (GI) bleeding has been observed in up to 60% of patients and makes up 23% of the causes of 30-day readmission, making it the most common reason for hospital readmission in CF-LVAD patients.[8] Thrombotic events are much less common with 2 year incidence rates ranging from 1.4% with HeartMate 3 and 6.4% with Heartware HVAD devices.[8]

Beyond hematologic complications, patients with left ventricular assist devices are prone to other complications, some which require procedural intervention.[9,10] Patients requiring procedural intervention may have prolonged stays in the hospital as providers allow a patient's INR to drift down, a process called watchful waiting.

To date, there have been limited studies evaluating the safety and efficacy of phytonadione (vitamin K) for patients with CF-LVADs. One study evaluated the efficacy of 100 mcg vitamin K with warfarin daily to help with INR control showing improved efficacy to reach therapeutic INR control.[11] There have been no studies evaluating the safety and efficacy of low-dose vitamin K for the reversal of INR in patients with CF-LVADs. The objective of this study was to assess the safety and efficacy of low-dose (<5 mg) vitamin K for reversal of INR in patients presenting with non-emergent bleeding or in need of urgent invasive procedures.

Methods

This was a single center, retrospective cohort analysis evaluating the safety and efficacy of low-dose vitamin K compared to watchful waiting. This study was approved by the Institutional Review Board. Patients were identified from the electronic health records (EHR). Patients were screened for a warfarin hold for a procedure and/or increased INR ($\geq$ 4 and <10). Time of hold and reason for hold were collected. Patients were divided into two groups: low-dose vitamin K and watchful waiting.

Patients were included if they had a CF-LVAD managed on warfarin, were admitted to undergo a non-life-threatening procedure that required interruption of their anticoagulation therapy, or had a supratherapeutic INR $\geq$4 and <10. Exclusion criteria included patients receiving vitamin K for a life-threatening complication (i.e. intracranial bleeding, blunt trauma), age <18, LVAD patients not managed on warfarin, cases of outpatient warfarin management complications

(i.e. INR ≥4 not requiring hospital visit), and patients that died during the encounter not due to one of the primary or secondary endpoints.

Data collected from the electronic medical record included demographic factors such as age on admission, race, and gender, LVAD type, serum creatinine, weight, height, presence of aspirin, presence of pentoxifylline, dipyridamole, or P2Y12 agent, length of stay, LDH, dose and route of vitamin K administered, procedure performed, INR on admission, INR on days 1, 2, and 3 after administration of vitamin K or watchful waiting, INR on discharge, thrombotic and bleeding events within 90 days after discharge, post-operative blood loss, and other products given (FFP, PRBC, Kcentra®). Missing INR values were interpolated using the Rosendaal method.[12]

The objective of this study was to assess the safety and efficacy of low-dose vitamin K (<5 mg), for reversal of INR in patients presenting with non-emergent bleeding or in need of invasive procedures. The primary endpoints included thrombotic and bleeding events within 90 days of discharge as a measure of safety and percentage of patients with an INR <2 within 24 hours of intervention as a measure of efficacy. Thrombotic events included deep vein thrombosis (DVT), pulmonary embolism (PE), pump thrombosis, and/or myocardial infarction. Bleeding events included subdural hematoma, subarachnoid hemorrhage, GI bleed, or intracranial hemorrhage. Secondary endpoints included length of hospital stay (days) and operative blood loss (mL) as a measure of bleeding.

Descriptive statistics were used to assess demographic factors, medications taken, pertinent lab values, and vitamin K doses and routes. The Mann-Whitney U test was used to analyze continuous non-parametric variables. The Fischer exact and chi-squared test was used to analyze categorical variables based on sample size. Data was reported as total counts and converted to percentages for each intervention or median with an interquartile range. Change in median INR between days 0,1,3, and discharge was assessed. Descriptive statistics were conducted in Microsoft Excel Version 2005 (Build 12827.20336) while all other analyses were conducted using R Studio Version 1.2.5001. A two-sided p-value of <0.05 was considered statistically significant.

Results

Patient Demographics and Study Population

A total of 84 LVAD patients with 121 patient-encounters which required INR reversal were evaluated. After exclusions, there were 13 patient-encounters in the vitamin K group and 34 patient-encounters in the watchful waiting group (Figure 1). Table 1 includes the baseline characteristics of the included patients. The median age of patients was 64 (IQR: 49-69) and 59.5 (IQR: 48-64) for the vitamin K and watchful waiting group respectively. African American male patients make up a majority of study population with 53.8% and 47.1% in the treatment and control group respectively. Patients in the vitamin K group received either 1 mg (46.2%) or 2 mg (53.8%) for INR reversal. Baseline INR was slightly higher in the treatment group (3.3)

compared to the control group (2.1). Different low-dose vitamin K doses were utilized with 46.2% being 1 mg IV and 53.8% being 2 mg IV. Concomitant medications included aspirin and pentoxifylline.

Measure of Safety

There were 0% and 23.5% thrombotic events (p = 0.085) in the vitamin K and watchful waiting group respectively (figure 2). Of the 8 thrombotic events in the watchful waiting group, 4 patients experienced a stroke, 3 experienced pump thrombosis, and 1 experienced a DVT. There were 5 and 4 bleeding events in the vitamin K and watchful waiting groups respectively (38.5% and 11.8%, p = 0.091). All of the bleeding events in the vitamin K group were gastrointestinal. The 4 bleeding events in the watchful waiting group included subdural hematoma, subarachnoid hemorrhage, GI bleed, and intracranial hemorrhage.

Measure of Efficacy

The length of stay between the groups was assessed in 5-day intervals for up to 30 days (Figure 3). In the vitamin K group, 38% of patients were discharged within 10 days and 21% in the watchful waiting group (p= 0.084). The number of days it took the INR to be <2 after intervention was assessed on days 0, 1, 2, 3, and at discharge (Figure 4). In the vitamin K group, 92% of patients achieved an INR <2 on day 2 compared to 56% in the watchful waiting group (p= 0.046). An INR decrease of 3.42 to 1.61 in the vitamin K group and 2.47 to 2.17 in the watchful waiting group (p = <0.01) was observed from day 0 after intervention to day 1 (Figure 5). The median INR on day 3 was 1.72 and 1.47 for the vitamin K and watchful waiting groups respectively with a p-value of 0.02. The median INR on discharge was 1.46 and 1.90 for the vitamin K and watchful waiting groups respectively p= 0.20).

Discussion

Thromboembolic and bleeding complications in LVAD patients are common. Non-emergent procedures such as endoscopies need INR reversal to prevent bleeding complications. Most cases target an INR <2 by holding warfarin and waiting for INR to come down to goal levels.[2] This can lead to increased length of hospital stay and infection risk leading to poor outcomes. Low-dose vitamin K has been hypothesized to decrease INR safely and effectively to reach goal INR levels faster. To our knowledge, this is the first study to evaluate safety and efficacy for the use of low-dose vitamin K for procedural INR reversal in LVAD patients.

Balancing bleeding and thrombotic risk in patients taking warfarin has been a challenge. Using vitamin K for INR reversal has been associated with thrombotic events due to over-correction of INR.[9] However, there was no significant increase in thrombotic events with low-dose vitamin K noted compared to watchful waiting suggesting less impact on INR over-correction . Though not significant, bleeding events occurred more in the low-dose vitamin K group. This may have been

due to those patients being at higher risk for bleeding due to prior GI bleeding events. Previous studies have also shown variability in GI bleeding with INR changes, suggesting slight variations in bleeding risk with lower INR values depending on the patient.[3] Operative blood loss was not assessed due to lack of reporting. Only 12 encounters between the groups reported operative blood loss making it difficult to analyze and assess the impact it may have had on bleeding. Based off the thrombotic and bleeding events noted, it can be suggested that the safety of low-dose vitamin K is comparable to watchful waiting.

Non-emergent procedures generally ask for an INR <2 to prevent excessive bleeding during the procedure. Patients receiving low-dose vitamin K achieved an INR <2 more quickly compared to the watchful waiting group ($p=0.046$). Thus, the results show that within 1 day of low-dose vitamin K administration, patients have lowered the INR to <2 allowing them to proceed with the procedure indicated and showing efficacy. However, length of hospital stay was not impacted ($p=0.08$) potentially due to a small sample size and complications of patients. Many patients required a non-emergent procedure but had to stay in the hospital afterwards for treatment. Other patients developed complications such as infections during their hospital course, requiring prolonged hospitalizations. Therefore, although low-dose vitamin K decreases time to procedure, the impact it has on overall hospital stay is limited. A more stable patient population stratified based off of comorbidities and complications can better assess length of hospitalization in a future study.

Limitations include small sample size, single-center experience, and retrospective study design. Due to the small sample size, it was difficult to balance comparator group for demographic factors, introducing confounding bias. The small sample size may have also contributed to a type II error suggesting some of the data may be significant if there were more samples. With these limitations, we suggest a prospective, randomized controlled trial powered for the primary endpoints of safety and efficacy. To increase study power for a prospective study, the number of vitamin K patients can be increased by lengthening study dates since low-dose vitamin K administration has become more prevalent at UNC Medical Center.

In conclusion, the data suggests vitamin K to be safe and effective for procedural INR reversal compared to watchful waiting in the LVAD population. A prospective, randomized, controlled study between low-dose vitamin K and watchful waiting is warranted to confirm the safety and efficacy of vitamin K.

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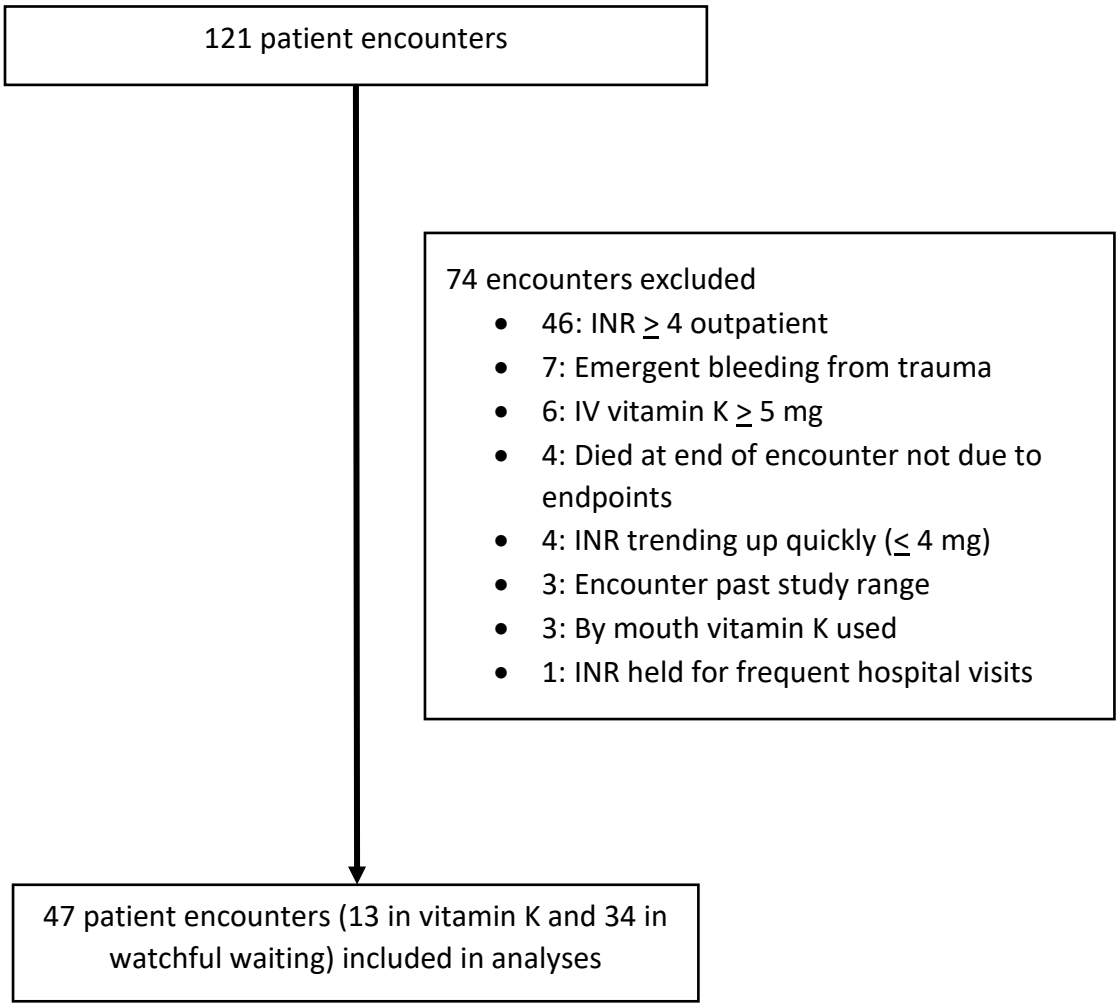
Figure 1: Patient Evaluation for Inclusion and Exclusion



INR = international normalized ratio; IV = intravenous; mg = milligrams

Table 1: Patient Baseline Characteristics, n = 47

	Vitamin K N = 13	**Watchful Waiting N = 34**	**P-value**
Median Age on admission, years (IQR)	64 (49-69)	59.5 (48-64)	0.512
Race, n (%)			0.840
Caucasian	5 (38.5)	15 (44.1)	
African American	7 (53.8)	16 (47.1)	
Other	1 (7.7)	3 (8.8)	
Gender, n (%)			0.257
Male	13 (100.0)	28 (82.4)	
Female	0 (0.0)	6 (17.6)	
Other Pertinent Medications, n (%)			0.412
Aspirin	7 (53.8)	17 (50.0)	
Pentoxifylline	3 (23.1)	3 (8.8)	
LVAD Type, n (%)			0.995
HeartMate II™	5 (38.5)	13 (38.2)	
HeartMate III™	6 (46.2)	15 (44.1)	
HeartWare HVAD®	2 (15.4)	6 (17.6)	
Baseline LDH (mg/dL), median (IQR)	573 (483-742)	748 (610-1069)	0.026
Baseline INR, median (IQR)	3.3 (2.7-4.5)	2.1 (1.6-3.1)	0.020
vitamin K dose, n (%)			<0.01
1 mg IV	6 (46.2)	N/A	
2 mg IV	7 (53.8)	N/A	

IQR = interquartile range; n = event frequency; LDH = lactate dehydrogenase; INR = international normalized ratio; IV = intravenous; mg = milligrams; p <0.05 is significant

Figure 2: Thrombotic and Bleeding Events (Percentage)

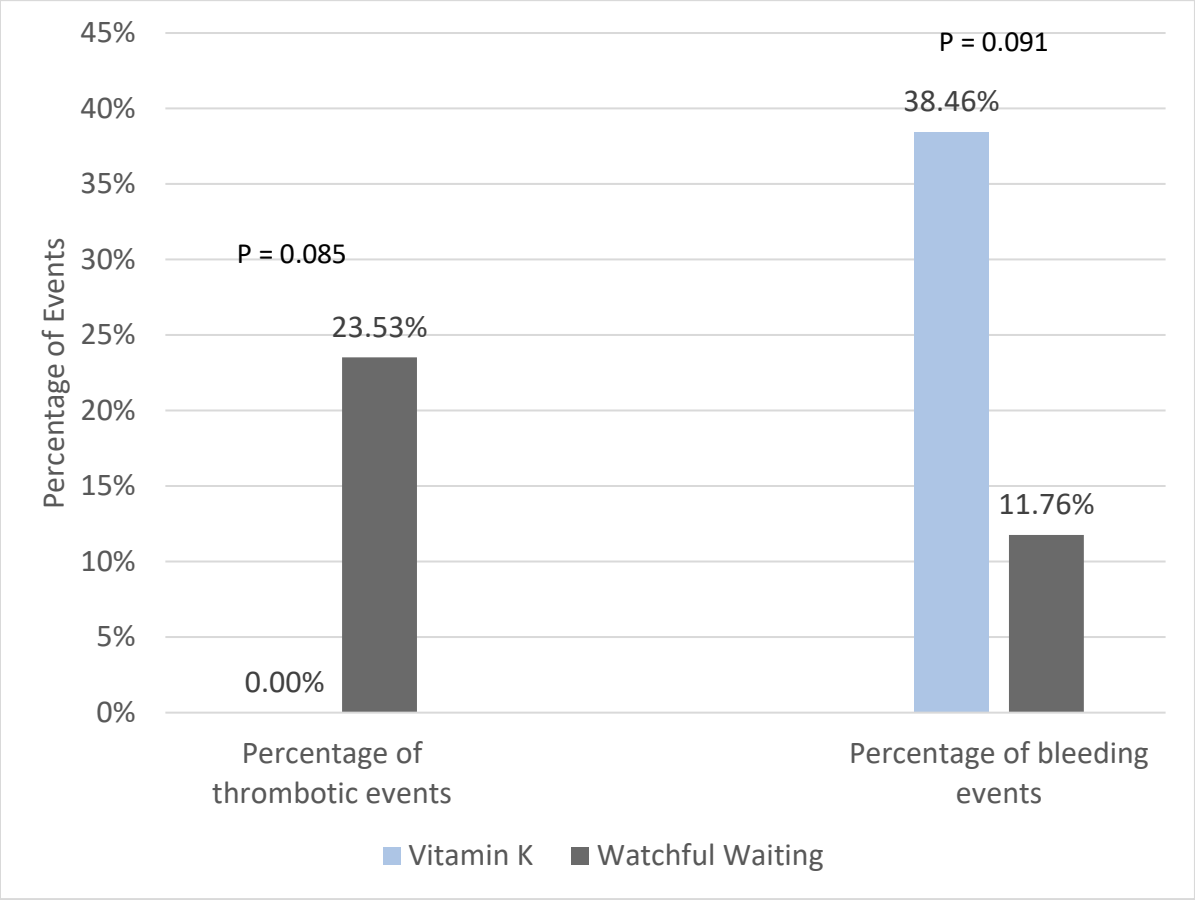


Figure 3: Days to Discharge (percentage)

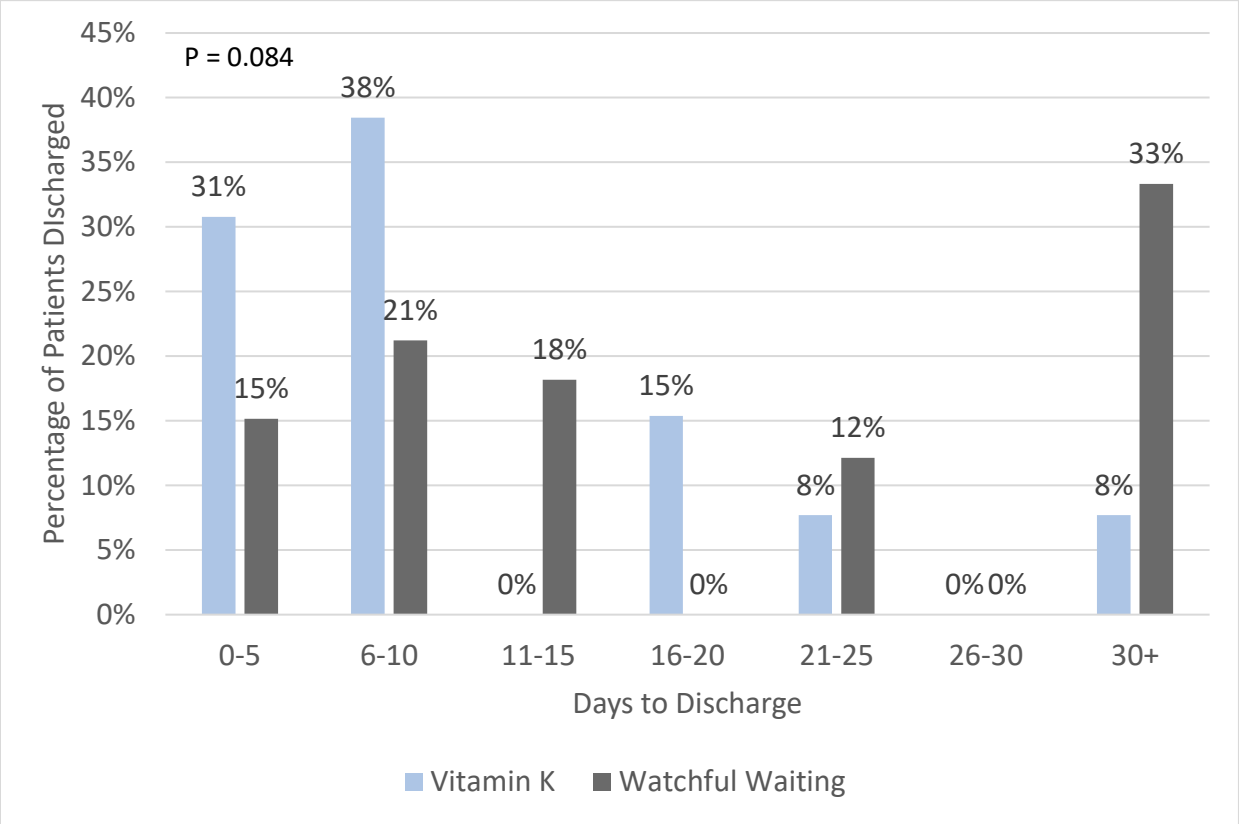


Figure 4: Time to INR <2 (percentage)

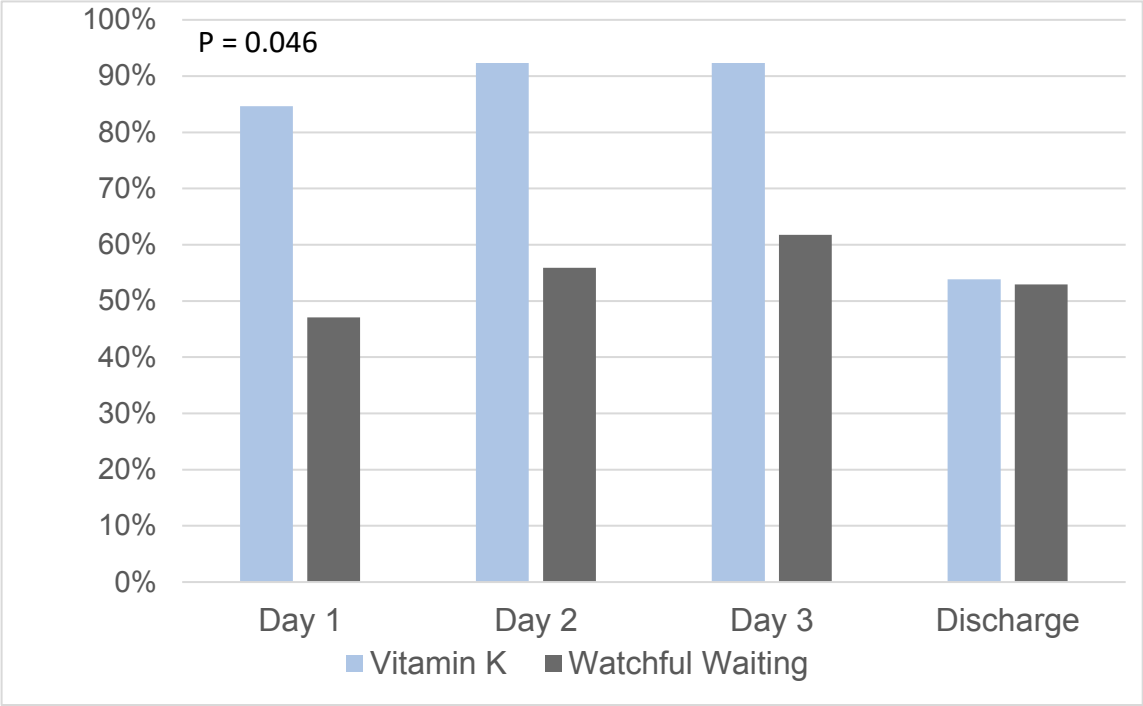
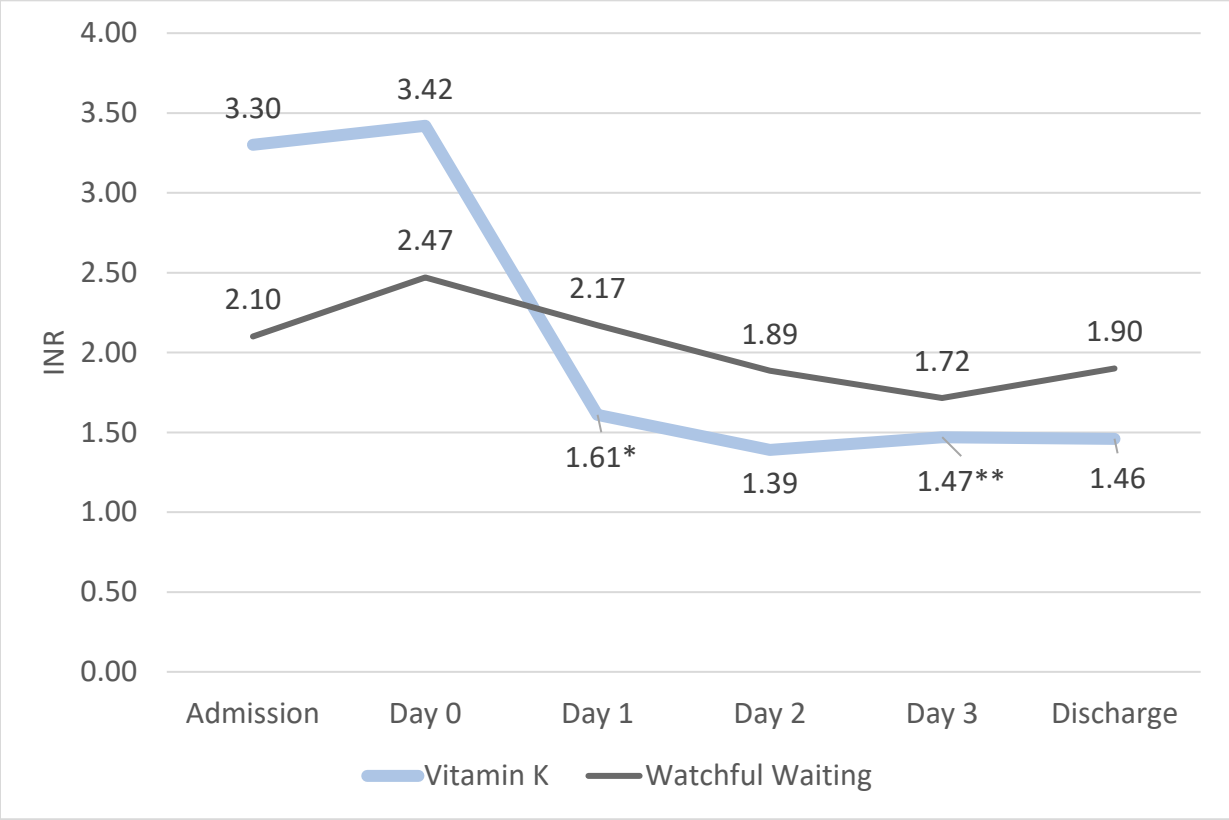


Figure 5: Median Change in INR from Admission to Discharge Between vitamin K and Watchful Waiting



*p for change in INR day 0-1: <0.01; **p for change in INR day 0-3: 0.02